UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,938	06/04/2002	Shinichiro Morita	SAEG108.001APC	4758

20995 7590 12/20/2007
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
NAFF, DAVID M

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
12/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/070,938
Filing Date: June 04, 2002
Appellant(s): MORITA ET AL.

C. Philip Poirier
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed Sept. 7, 2007 appealing from the Office action mailed March 12, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference

characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because the summary of the invention (bridging pages 2 and 3 of the brief) describes a matrix for culturing cardiovascular cells to regenerate cardiovascular tissue, and not the claimed method of using the matrix for regenerating cardiovascular tissue. The method is carried out by seeding cells on the matrix configured to regenerate cardiovascular tissue, culturing the cells until the matrix surface is completely covered with the cells, and embedding the matrix *in vivo* for regenerating cardiovascular tissue (specification, page 5, line 12 to page 7, line 22, and page 12, line 1 to page 13, line 14). The matrix used in the method comprises a sponge configured to regenerate cardiovascular tissue, and is made of bioabsorbable material and a reinforcement made of a bioabsorbable material integrated with the sponge and located

inside or on the exterior surface of the matrix (specification, page 4, line 1 to page 5, line 11, page 6, line 17 to page 7, line 22, and page 8, lines 13-22).

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection under 35 USC § 112, second paragraph, and the rejection of dependent claim 10 under 35 USC § 103.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,855,610	Vacanti et al	1-1999
6,534,084	Vyakarnam et al	3-2003 (filed 6-1999)
5,863,531	Naughton et al	1-1999
JP 3-23864	Japan	1-1991

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9, 11 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vacanti et al in view of Vyakarnam et al and the Japanese patent.

The method claimed is described above under "Summary of Claimed Subject Matter".

Vacanti et al disclose reconstruction and augmentation of flexible, strong connective tissue such as arteries and heart valves (col 1, lines 4-7). Objectives include producing tissue engineered constructs having improved mechanical strength and flexibility, making valves and vessels which can withstand repeated stress and strain, and improving yields of engineered tissues (col 2, lines 33-42). Structures are created by seeding

a fibrous or porous polymeric matrix with cells (col 2, lines 65-67) to form tissues having structural elements such as heart valves and blood vessels (col 3, line 2-3). For a tissue to be constructed, successfully implanted and function, matrices must have sufficient surface area and exposure to nutrients such that cellular growth and differentiation can occur prior to the ingrowth of blood vessels following implantation (col 3, lines 26-29). The matrix acts as a scaffold providing a three-dimensional space for cell growth. The matrix functions as a template providing structural cues for tissue development (col 3, lines 10-15). The scaffold determines the limits of tissue growth and thereby determines the ultimate shape of a tissue engineered construct. The cells on the matrix proliferate only to the edges of the matrix (col 3, lines 20-23). The matrix can be formed of polymers having a fibrous structure, which has sufficient interstitial spacing to allow for free diffusion of nutrients and gases to cells attached to the matrix surface. The spacing can be in a range of 100 to 300 microns, although closer spacings can be used if the matrix is implanted, blood vessels are allowed to infiltrate the matrix, then the cells are seeded into the matrix (col 3, lines 42-49). The matrix can have pores in a range of approximately between 100 and 300

microns (col 3, line 57). The matrix can be sponge like (col 3, line 51), and can be a polyvinyl alcohol sponge (col 4, lines 25-27). The matrix can be formed of a biodegradable polymer such as poly(lactide) (PLA), poly(glycolic acid) (PGA) or poly(lactide-co-glycolide) (PLGA) (col 4, lines 8-11). Forms of lactic acid used to prepare PLA polymers can be L(+), D(-) or DL (col 4, lines 45-49). While not preferred, a natural polymer such as collagen can be used to form the matrix (col 4, line 35). The overall matrix configuration is dependent on the tissue, which is to be constructed or augmented. The shape of the matrix can be obtained using struts that impart resistance to mechanical forces to yield the desired shape such as heart valve leaflets and tubes (col 3, lines 62-67, and col 5, lines 35-48). The struts can be biodegradable, and formed of the polymer material used to form the matrix to provide a matrix having sufficient strength to resist the necessary mechanical forces. In Example 1 (beginning in col 7, line 60), a tissue engineered heart valve is produced. A PGA fiber based matrix is seeded with a mixed cell population containing myofibroblasts and endothelial cells and grown in culture until the myofibroblasts reached confluence (col 8, lines 9-15). Then endothelial cells are seeded onto the surface of the

fibroblast/mesh construct and grown into a single monolayer. The tissue engineered heart valve resembled native valve tissue. The construct was implanted in sheep to determine if the construct had the required pliability and mechanical strength (col 8, lines 21-23). In Example 2 (beginning in col 8, line 45), a tissue engineered vascular structure is prepared. A PGA tubular construct is seeded with a smooth muscle cells and fibroblasts. After the fibroblasts and smooth muscle cells have grown to confluence, endothelial cells are seeded on the construct and the construct placed in culture (col 8, lines 50-56). Endothelially lined smooth muscle/fibroblast tubes were created (col 9, lines 5-7). Vacanti et al disclose producing blood vessels, arteries and heart valves (cardiovascular tissue) using steps as claimed by seeding cells on a matrix made of bioabsorbable material configured to regenerate the tissue, culturing the cells on the matrix (Examples 1 and 2), and embedding the matrix *in vivo*, i.e. implanting the matrix containing tissue formed (col 2, lines 41-42, and col 8, line 21).

The Japanese patent discloses (see translation) (page 1, under "Background Art") that in the surgical treatment of wounds or defects and in orthopedic surgery, filler material is

embedded in damaged areas in order to regenerate tissue and prevent contracture. The filler material is required to have little reactivity with tissue, promote the proliferation of fibroblasts and maintain strength and shape over a long period until tissue is regenerated. A particularly required property of the filler material is to maintain shape to prevent contracture of tissue, and disappear within the body not to remain as a foreign object after tissue is formed. Microporous collagen sponges have been proposed for such purposes, but do not have the required properties, i.e. glutaraldehyde cross-linked collagen sponges do not maintain the requisite long-term shape and strength for use in treatment, and within two to three months of implantation in the body, are completely broken down and absorbed by the body (page 2, under "Problem to be Solved by the Invention"). The problem is solved (page 2, under "Solving the Problem) by providing a composite material consisting of collagen sponge and a biodegradable fibrous poly-L-lactic acid mixed into or embedded in the collagen sponge. Combining the poly-L-lactic acid, which is slow to degrade within the body, with collagen sponge, makes it possible to maintain structural pores of the sponge over a long period of time, and to promote the propagation of fibroblasts in the interior of the composite

material, and maintain the strength and shape over a long period of time required for treatment (paragraph bridging pages 2 and 3). In the embodiment described (page 3), a composite is prepared containing poly-L-lactic acid fibers embedded in microporous collagen sponge. Table 1 (bottom of page 3) shows the composite (present invention) having strength of 7.7, whereas glutaraldehyde cross-linked collagen sponge (comparative example) has a strength of only 1.3. The composite has the required properties for use, and does not react with tissue, promotes the propagation of fibroblasts, maintains strength and shape over a long period of time until tissue is regenerated, prevents contracture of tissue, and is broken down and absorbed by the body after the regeneration of tissue (page 5, second complete paragraph).

Vyakarnam et al disclose foam structures that can be composed of copolymers of lactide such as a poly(L) lactide-co-E-caprolactone (col 6, line 45, col 9, lines 53-55 and col 12, lines 5-9), and which can be used to regenerate tissue such as tubular structures such as vascular grafts (col 3, lines 1 and 20-21, and col 9, lines 19-24). The pore size of the foam can be 30-50 Tm or 100-200 Tm (paragraph bridging cols 4 and 5).

The foam can be reinforced with fibers (col 6, line 40) made of calcium phosphate.

It would have been obvious to use a sponge containing embedded fibers for reinforcement as the matrix of Vacanti et al for engineering tissues to obtain the function of the fibers in the sponge to maintain strength, shape and structural pores of the sponge as suggested by the Japanese patent and Vyakarnam et al since Vacanti et al disclose that the matrix can be sponge-like (col 3, line 51), or can be a polyvinyl alcohol sponge (col 4, lines 25-26). Fibers in the sponge are integrated with the sponge, and blood vessels, arteries and heart valves produced by Vacanti et al are cardiovascular tissue. The function of the fibers to maintain strength, shape and structural pores of a sponge as taught by the Japanese patent and to reinforce a foam as taught by Vyakarnam et al would have been motivation to use a sponge containing embedded fibers for reinforcement. The fibers would have been expected to provide the function of strength to resist mechanical forces and maintain a desired shape provided by the struts of Vacanti et al, or in combination with the struts, to provide additional strength to resist mechanical forces. Growing cells to confluence and forming a monolayer of endothelial cells on the matrix as in Example 1 of Vacanti et al

(col 8, lines 12-15) will produce a matrix completely covered with cells as required in claim 7. Growing cells to confluence and culturing as in Example 2 of Vacanti et al will also result in the matrix completely covered with cells. Producing a blood vessel, as in claim 8 and a cardiac valve as in claim 9, is disclosed by Vacanti et al (Examples 1 and 2). In Examples 1 and 2, Vacanti et al use a mixed cell culture (col 8, lines 8 and 49-50) as in claim 11. Vacanti et al disclose using materials that are bioabsorbable (col 4, lines 9-15 and 41-49) as in claim 15. A pore diameter in the range of about 5 microns to about 100 microns in claim 19 would have been obvious from Vacanti et al disclosing pores in a range of between approximately 100 and 300 microns (col 3, line 57). Using polylactic acid or polyglycolic acid to prepare the fibers as in claims 16-18, would have been obvious from the Japanese patent disclosing fibers made from poly-L-lactic acid embedded in a sponge, and Vacanti et al disclosing poly(lactide) (PLA) and poly(glycolic acid) (PGA) as biodegradable polymers that can be used to form the struts and sponge (col 4, line 9 and col 5, lines 45-47). It would have been further obvious to use lactic acid-caprolactone copolymer to form the sponge as in claims 16-18 since Vacanti et al disclose that the matrix can be formed of

poly(caprolactone) (col 4, lines 9-11) and Vyakarnam et al disclose foam structures such as vascular grafts formed of poly(L) lactide-co-E-caprolactone (col 6, line 45) for use in tissue engineering.

Claim Rejections - 35 USC § 103

Claims 7, 8 and 11 are are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (5,863,531).

The claimed invention is described above.

Naughton et al disclose producing tissue *in vitro* by seeding cells on a three-dimensional framework having interstitial spaces, which can be shaped to assume the conformation of natural organs and their components (col 4, lines 63-64). The three-dimensional framework can be formed of biodegradable matrices such as collagen sponge (col 9, line 42), or polyglycolic acid or polylactic acid and copolymers thereof (col 9, lines 59-62). Tubular tissue structures can be formed (col 6, lines 55-60 and col 22, line 41) such as in the form of blood vessels (col 24, line 33), arteries (col 24, line 37) or veins (col 25, line 24). Implantation of a valve is also disclosed (col 19, line 49). Stromal cells such as fibroblasts or stromal cells in combination with other cells such as

endothelial cells or smooth muscle cells (col 4, lines 23-28, and col 11, lines 9-25) are grown *in vitro* on the framework where the stromal cells and their naturally secreted extracellular matrix proteins and connective tissue proteins envelop the framework to form a three dimensional living stromal tissue (col 4, lines 30-44, col 7, lines 51-60, and col 11, line 64). Since the inner walls of arteries are rich in elastin, an arterial stroma should contain a high concentration of smooth muscle cells which elaborate elastin (col 13, lines 28-31). The elastin provides strength and elasticity required of blood vessels *in vivo* (col 4, lines 2-9). Once the three dimensional tissue has reached the appropriate degree of growth, tissue-specific cells are inoculated on the stromal tissue, and can be grown on the stromal tissue *in vitro* to form a cultured counterpart of the native tissue prior to implantation *in vivo* (paragraph bridging cols 13 and 14, and col 14, lines 5-10). The cells chosen for inoculation depend on the tissue to be produced such as epithelium, endothelium and smooth muscle (col 14, lines 13-16). When producing arties, fibroblast cells and smooth muscle cells can be cultured to subconfluence on separate frameworks, the frameworks combined and the smooth muscle cells proliferated to produce elastin to simulate natural arterial

walls. Thereafter, endothelial cells are seeded on top of an upper, elastin-rich layer, and incubated until they form a confluent layer (paragraph bridging cols 24 and 25, and col 25, lines 11-15).

When producing tubular tissue structures such are arteries, veins, blood vessels that are cardiovascular tissue as disclosed by Naughton et al, it would have been obvious to use collagen sponge as the framework in which cells are cultured to produce the tissue as suggested by Naughton et al (col 9, line 60). The extracellular matrix containing elastin produced during culturing stromal cells will result in the extracellular matrix being integrated with the sponge and functioning for reinforcement of the sponge prior to seeding the sponge with tissue specific cells. Naughton et al disclose that elastin is a necessary component of blood vessels and provides strength (col 4, line 5) to the vessels, and is normal component of arteries (col 13, lines 28-31). After culturing tissue-specific cells on the stromal tissue contained by the collagen sponge, the sponge surface will be completely covered with cells since Naughton et al disclose that the tissue produced is a counterpart of native tissue prior to implantation (col 14, lines 7-10), and disclose culturing seeded endothelial cells on

a elastin-rich layer to form a confluent layer (col 25, lines 13-15). A collagen sponge that is not completely covered with tissue formed by culturing the tissue-specific cells will not be a counterpart of native tissue. Naughton et al suggest a blood vessel (col 24, line 33) as required by claim 8, and a mixed cell culture (col 8, lines 16-17, and col 11, lines 9-15) as required by claim 11.

Claim Rejections - 35 USC § 103

Claim 9, 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al as applied to claims 7, 8 and 11 above, and further in view of Vacanti et al.

The claimed invention, Naughton et al and Vacanti et al are described above.

It would have been obvious to use the procedure of Naughton et al to produce a heart valve as in claim 9 in view of Vacanti et al producing vascular structures or heart valves by a procedure similar to that of Naughton et al. Using bioabsorbable polymers of claim 15 to produce the sponge instead of from collagen would have been suggested by Vacanti et al using such materials to produce a biodegradable sponge-like matrix for engineering tissue. A pore size in the range of claim 19 would been obvious from Vacanti et al disclosing pores

in a range of approximately between 100 and 300 microns (col 3, line 57).

Claim Rejections - 35 USC § 103

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 9, 15 and 19 above, and further in view of Vyakarnam et al and the Japanese patent.

The invention and references described above.

When using bioabsorbable polymers instead of collagen to prepare a sponge for use as the framework of Naughton et al as suggested by Vacanti et al as set forth above, it would have been obvious to use lactic acid-caprolactone copolymer as the polymer as suggested by Vacanti et al disclosing that the sponge-like matrix can be formed of poly(caprolactone) (col 4, line 11), and Vyakarnam et al disclosing foam structures such as vascular grafts formed of poly(L) lactide-co-E-caprolactone for use in tissue engineering. Providing fibers made of polylactic acid or polyglycolic acid for reinforcement in the sponge made of lactic acid-caprolactone copolymer would have been suggested by Vyakarnam et al and the Japanese patent for the type of reasons set forth above when applying these references to suggest fibers for reinforcement in a sponge.

(10) Response to Argument

Response to Arguments

Appellants urge (paragraph bridging pages 3 and 4 of the brief) that it has been discovered that when an unreinforced material is employed, the resulting graft can fail catastrophically. However, an unreinforced sponge failing would not have been unexpected in view of Vacanti et al using struts to resist mechanical forces to maintain a desired shape of a sponge-like matrix used for tissue engineering, the Japanese patent using fibers embedded in a sponge to maintain shape and strength and structural pores of the sponge when used for implanting in damaged areas of wounds and defects, and in orthopedic surgery, and Vyakarnam et al using fibers to reinforce a foam used for repair and regeneration of tissue. Therefore, it is apparent that failure of an unreinforced sponge was a known problem when engineering a cardiovascular graft at the time of the present invention, or otherwise Vacanti et al would not have disclosed using struts to resist mechanical forces, the Japanese patent would not have disclosed using fibers embedded in a sponge to maintain strength, shape and structural pores of the sponge, and Vyakarnam et al would not have disclosed using fibers to reinforce a foam structure. The

references clearly indicate that Appellants were not the first to discover that failure of a graft can occur when a sponge used to form the graft is not reinforced.

Appellants refer to pages 12-13 (Example 1) of the present specification as showing failure occurring when using an unreinforced material as compared to using a reinforced material. However, the present claims do not require a vascular matrix constructed as in the example and implanting in the inferior vena cava of a dog as in the example. The claims encompass a matrix constructed substantially different from that used in the example, and such substantially different matrix could have failed when implanted under conditions of the example. Whether a reinforced matrix fails will depend on how the reinforced matrix is constructed and the kind of mechanical forces the reinforced matrix is subjected.

Appellants urge that the struts of Vacanti et al are not integral with the sponge nor inside or on the exterior surface of the matrix. However, fibers embedded in a sponge as suggested by the Japanese patent and Vyakarnam et al for reinforcement will be inside the sponge and integral with the sponge. The rejection is not based on using only the struts of Vacanti et al for reinforcement, but on using fibers embedded in

the sponge to provide reinforcement as suggested by the Japanese patent and Vyakarnam et al.

Appellants urge that having reinforcement integrated with the sponge either inside or outside the sponge provides a smooth sponge surface coming in contact with blood flow. However, the present claims do not require contacting the reinforced sponge with blood flow. In any event, when using fibers inside the sponge as suggested by the Japanese patent and Vyakarnam et al for reinforcement, the sponge will have a surface as contained by the reinforced sponge of the claims.

Appellants urge that Vyakarnam et al does not disclose reinforcement inside or on the exterior of the matrix. However, Vyakarnam et al is combined with the Japanese patent which discloses fibers embedded in a sponge for reinforcement, and when both references are considered together in combination, it would have been obvious to provide the reinforcement inside the sponge. Vyakarnam et al contain no disclosure that the fibers be implanted separate from the foam, or that the fibers are not be embedded in the foam like the fibers of the Japanese patent are embedded in a sponge.

Appellants urge that the disclosure of Vyakarnam et al does not relate to tissue engineering. However, from a reading of

the title, abstract, specification and claims of Vyakarnam et al, it will become apparent that the disclosure of Vyakarnam et al does relate to tissue engineering. Vyakarnam et al disclose regenerating tissue of tubular structures such as vascular grafts (col 3, lines 1 and 20-21 and col 9, lines 19-24). Appellants refer to Vyakarnam et al providing stiffness. However, the present claims do not exclude a certain amount of stiffness, and do not require the matrix embedded *in vivo* to have a certain amount of pliability.

Appellants urge that there is no reason to combine the Japanese patent (Morita et al) with Vacanti et al or Vyakarnam et al. While the Japanese patent may not seed and grow cells in the sponge before implanting, this reference is combined with the Vacanti et al and Vyakarnam et al references which suggest seeding and growing cells prior to implanting. It would have been obvious that the reinforced sponge of the Japanese patent can be seeded with cells and the cells grown prior to implanting since the sponge is similar to the sponge-like structure of Vacanti et al and the foam of Vyakarnam et al. The Japanese patent discloses the need to maintain structural pores of the sponge to promote propagation of fibroblasts in the interior of

the sponge (paragraph bridging pages 2 and 3 of the translation).

Appellants urge that the Japanese patent does not suggest reinforcement after fully regenerated tissue is present. However, the present claims do not requirement reinforcement after tissue is fully regenerated. The reinforced sponge of the claims can bioabsorb in the same amount of time as the reinforced sponge of the Japanese patent.

Appellants urge that unexpected results of the invention have been discounted. However, as set forth above, the references indicate that the problem of graft failing when not prepared from an unreinforced sponge was known. The claims are not limited to the specific construction of a vascular regeneration matrix and conditions of its use under which failure did not occur as shown by Example 1 in the specification.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

David M. Naff
Primary Examiner
Art Unit 1657

Conferees:

Jon P. Weber

Jon Weber
Supervisory Patent Examiner

Michael G. Wityshyn

Michael G. Wityshyn
Supervisory Patent Examiner
Technology Center 1600